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**A NEW ORAL IMMEDIATE RELEASE DOSAGE FORM****FIELD OF THE INVENTION**

- 5 The present invention relates to an oral immediate release dosage form of a pharmaceutically active compound, *N*-[(1,2,3,4-tetrahydro-5-methyl-8-(4-methylpiperazin-1-yl)-2-naphthyl]-4-morpholinobenzamide, in the form of the free base or pharmaceutically acceptable salts thereof. The invention further relates to processes for preparing said dosage form and the use of said dosage form in therapy such as prevention  
10 and/or treatment of disorders in the CNS and related disturbances.

**BACKGROUND OF THE INVENTION**

- 15 The development of new pharmaceutical active compounds is often hampered or even blocked due to unwanted physico-chemical properties of these new active compounds. Some of the properties may be overcome by developing suitable pharmaceutical formulations. This is for example true for compounds that form a hydro gel upon contact with water and/or intestinal fluids. An active compound that forms a gel upon contact with  
20 water cannot become rapidly available after administration. Such a delay in release of the active compound results in a delay of onset of action of the active compound.  
*N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide is an active compound that forms a gel upon contact with water. *N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide may be used in the prevention and/or treatment of disorders and  
25 related disturbances in the central nervous system (CNS).  
Formulating *N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide in a pharmaceutical composition has been difficult due to the fact that a gel is formed upon contact with water. The use of excipients such as binders, e.g. hydroxypropyl cellulose, microcrystalline cellulose and gelatine and the like and fillers  
30 such as lactose, microcrystalline cellulose, dibasic calcium phosphate do not prevent the

active compound from forming a gel. The gel forming properties of the active compound make it difficult to prepare an immeidated release dosage form of this active compound.

It has now surprisingly been found that disintegrants, especially the so called super-disintegrants, are useful in the preparation of dosage forms of gel forming active compounds such as *N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide. It is believed that disintegrants shield the active compound from water and thereby prevent the active compound from forming a gel. By using disintegrants the dosage form disintegrates in small granulate particles upon contact with water, thereby making the active compound readily available after administration without any gel being formed of the active compound.

Disintegrants are known for their wicking capacity to channel water into the interior of a pharmaceutical composition and rapidly swell in water, thereby hasten the disintegration of the active compound.

15 Disintegrants have been used in pharmaceutical compositions like flash-melt compositions to increase the disintegration of pharmaceutical compositions.

EP 1145711 describes a flash-melt composition comprising an active compound, a disintergrant, a dispersing agent, a distribution agent and a binder. This pharmaceutical composition dissolves within 25 seconds in the mouth.

WO 01/76565 discloses a fast disintegration composition comprising a disintegrant, a filler, a sugar alcohol and a lubricant. This composition dissolves within 90 seconds in the mouth.

25 WO 01/12161 discloses a process for the manufacturing of a rapid dissolving dosage form that dissolves within 30 seconds in the mouth.

The multifunctional use of disintegrants has also been described.

In WO 02/03987 disintegrants have been used to increase the stability and dissolution of poorly-soluble drugs.

30 In WO 00/02536 describes the use of disintegrants as a disintegrant and as a taste-masker. The active compound is coated with the disintegrant to cover the bitter tast of the active compound.

JP 10114655 discloses a solid preparation of an active compound that forms a gel in an acidic solution. Disintegrants are used to prevent the active compound of forming a film on the surface of the acidic solution.

5

The problems in obtaining a solid oral immediated release dosage form comprising an active compound such as *N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide, that forms a gel upon contact with water, has not been addressed well in the prior art.

10

There is still a need for a suitable solid oral immediated release dosage form of active compounds, that forms a gel upon contact with water, at acid, neutral and basic pH, whereby the dosage form provides a rapid release of the active compound (e.i. within 30 minutes) after administration in mammals.

15

Further, the fact that the active compound forms a gel upon contact with water makes the compounds difficult to handle during the preparation of the dosage form.

15

This is especially true for large-scale production of immediated release oral dosage forms such as capsules and tablets.

20

We have now surprisingly found that disintegrants may be used to prepare a solid dosage form comprising a gel forming active compound such as *N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide. In the present invention disintegrants are used to shield the active compound from water, thereby preventing it from forming a gel and thus making it possible to have the active compound, *N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-

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morpholinobenzamide, readily available after administration of the dosage form.

Further, disintegrants prevent the active compound from forming a gel during the preparation process, even at large-scale production.

#### DETAILED DESCRIPTION OF THE INVENTION

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The present invention provides for a solid oral immediated release dosage form that is especially suitable for, in an aqueous environment, gel forming active compound. The oral

immediated release dosage form comprises an active compound, at least one disintegrant, at least one binder, and optionally other excipients, whereby the amount of the active compound may be up to 35% (w/w).

The oral dosage form of the present invention provides for a rapid release profile of the active compound *in vivo* having a rapid initial rise in blood plasma concentration thereby providing a fast onset of effect of the active compound. Compared to an immediated release dosage form that does not comprise a disintegrant, the present invention provides for a dosage form having less fluctuations of the intra patient-patient blood plasma concentration and thus less risk for plasma concentrations being outside the therapeutic window.

Active compounds that are specifically suitable to use in the present invention are pharmaceutically active compounds with a gel forming tendency, in an aqueous environment, at any pH.

In one aspect of the invention the oral immediated release dosage form comprises as active compound, *N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide in the form of the free base or pharmaceutically acceptable salts thereof.

A further aspect of the present invention relates to the oral immediated release dosage form comprising as active compound, (*R*)-*N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide.

Particularly suitable is the monohydrobromide salt of (*R*)-*N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide. (*R*)-*N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide monohydrobromide is slightly soluble in water (6.4 mg/ml), sparingly soluble in ethanol/water 1:1 (19 mg/ml) and sparingly soluble in 0.1 M HCl (11 mg/ml). (*R*)-*N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide monohydrobromide has a plasma elimination half-life, *t<sub>1/2</sub>*, of 35 hours. (*R*)-*N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide monohydrobromide has shown to have at least five crystal modifications, named A, B, C, D and E. Any of these crystal forms A, B, C, D and E may be used in the preparation of the dosage form of the present invention. Form A is an anhydrate and ansolvate form and is the preferred crystal form.

- The present invention relates to an oral immediated release dosage form comprising *N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide as the active compound, in the form of the free base or pharmaceutically acceptable salts, thereof, at least one disintegrant, at least one binder, and optionally other excipients.

More specifically, the present invention relates to an oral immediated release dosage form comprising

<i>N</i> -[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide	3 to 35 % (w/w)
Disintegrants	5 to 20% (w/w)
Binders	1 to 10 % (w/w)
Other excipients	up to 100% (w/w)

- 10 The dosage form of the invention shall contain at least one disintegrant selected from the group of carboxymethylene celluloses. For example, the disintegrant is the salt of crosslinked carboxymethylene cellulose such as a salt of an alkaline earth metal, e.g. the sodium salt.
- 15 The invention relates to the oral immediated release dosage form, whereby the disintegrants are selected from the group consisting of croscarmellose sodium, sodium starch glycollate, crospovidone, microcrystalline cellulose, soy polysaccharide, starch, alginic acid, magnesium aluminium silicate and amberlite resins.  
The invention further relates to the oral immediated release dosage form wherein the disintegrant is croscarmellose sodium.
- 20

Effervescent excipients such as citric acid, ascorbic acid or tartaric acid in combination with sodium- or potassium carbonate or -bicarbonate, may also be used in the oral immediated release dosage form.

The amount of disintegrants in the immediated release dosage form of the present invention may be in the range from 1 to 40% (w/w), preferably 5 to 20% (w/w).

The weight ratio of active compound to disintegrants in the oral immediated release dosage form of the present invention, may be from 5:1 to 1:2, preferably from 3:1 to 1:1.

5

In one aspect of the invention the oral immediated release dosage form comprises binders selected from the group comprising of hydroxypropyl cellulose, microcrystalline cellulose, polyvinylpyrrolidone, gelatine, polyethylene glycol, glycerylbehenate, glycerylmonostearate and carnauba wax or a mixture thereof.

10 A suitable binder is polyvinylpyrrolidone with an average molecular weight between 25.000 and 30.000.

The amount of binders in the immediated release dosage form of the present invention may be in the range from 0 to 20 % (w/w), preferably 1 to 10% (w/w).

15 The weight ratio of active compound to binders may be from 8:1 to 1:2, preferably from 7:1 to 1:3.

Beside the disintegrants and binders, the oral immediated release dosage form may optionally comprise other excipients, such as lubricants, release modifying agents, flow condition agents and the like.

20

In one aspect of the invention the oral immediated release dosage form comprises lubricants selected from the group of magnesium stearate powder, sodium stearyl fumarate, stearic acid, polyethylene glycol and talc.

25

In one aspect of the invention the oral immediated release dosage form comprises release modifying agents selected from the group of lactose, mannitol, sorbitol, calcium phosphate, aluminium silicate, paraffin, carboxypolyethylene, carboxyvinyl polymer, acrylic acid polymer, ethyl cellulose and polyethylene glycol.

30

In one aspect of the invention the oral immediated release dosage form comprises flow condition agents such as e.g. colloid silicon dioxide.

The amounts of these other excipients in the immeidated release dosage form of the present invention may be in the range of 35 to 91 % (w/w).

- The dosage form may be prepared by mixing the active compound, the disintegrants, binders and optionally other excipients such as lubricants, release modifying agents and flow condition agents and the like in a suitable mixer, e.g. a Turbula mixer. The dry mix may then be filled directly into an oral dosage form.
- Another route is to compress said homogeneous mixture comprising the active compound, the disintegrants and the binders. These compacts may be milled through a screen and finally mixed with additional excipients such as lubricants, release modifying agents, flow condition agents and the like and filled into an oral dosage form.
- Alternatively, the dosage form may be prepared from a granulated powder. A homogeneous powder mixture may be obtained by mixing the active compound, the disintegrants and optionally excipients such as binders in a suitable mixer. The mixture may then be granulated in water or another granulation liquid such as an alcohol, e.g. ethanol, methanol, isopropanol, a ketone, e.g. acetone or aqueous mixtures thereof. From an environmental point of view water is preferred. The resultant wet granulation may thereafter be dried in a drying cabinet or in a fluid bed dryer and milled through a screen. The granulation may also be performed at elevated temperatures by using meltable binders.
- The cooled granulation may be milled through a screen. The dry granulated powder mass is then mixed with other excipients and filled into a suitable oral dosage form.
- Suitable oral dosage forms are e.g. tablets, capsules, compacted tablets, minitablets and the like.
- The present invention relates to an oral immeidated release dosage form, wherein the dosage form is in the form of a tablet or a capsule.
- The present invention also relates to processes for the manufacture of the immeidated release dosage form characterized by,
- method A, comprising the steps:
- Ai) mixing the active compound with the disintegrant, binders and optionally lubricants, release modifying agents and other excipients,

Aii) forming the obtained dry powder mixture into a suitable solid dosage form,  
or,

**method B, comprising the steps:**

s Bi) mixing the active compound with the disintegrant and optionally binders and other excipients,

Bii) granulating said mixture,

Biii) optionally drying the obtained granules,

Biv) mixing the granules with other excipients,

Bv) filling the obtained dry powder mixture into suitable solid dosage form.

10

Further, the present invention relates to an oral immediated release dosage form which has an *in vitro* dissolution profile in 50 mM acetate buffer, pH 5.5 with apparatus 2 described in USP 24, paddle method at 75 rpm, such that 80 % or more of the active compound is released within 30 minutes.

15

The composition from which the dosage form is prepared can be formulated to contain the active compound in different amounts, e.g. between 1 and 100 mg, preferably between 5 and 50 mg, but is not limited to these intervals. These figures are presented as the free base. Suitable daily doses of the active compound may vary within a wide range and will depend on various factors such as the relevant disorder or medical conditions, the age, weight and sex, and may be determined by a physician.

The oral immediated release dosage form of the invention may thus comprise

N-[5-methyl-8-(4-methylpiperazin-1-yl)-	3 to 35 % (w/w)
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1,2,3,4-tetrahydro-2-naphthyl]-4-	
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morpholinobenzamide	
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Disintegrants	5 to 20% (w/w)
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Binders	1 to 10 % (w/w)
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Lubricants	0 to 2 % (w/w)
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Flow condition agents	0 to 2 % (w/w)
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Release modifying agents	up to 100% (w/w)
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Int'l Patent Office register

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### Medical and Pharmaceutical Use

One aspect the present invention provides the use of the oral immediated release dosage

5 form in therapy. *N*-[5-methyl-8-(4-methylpiperazin-1-yl)-  
1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide may be used as a h5-HT 1B  
antagonists, partial agonists or full agonists, preferably as antagonists. Therefore, the oral  
immediated release dosage form comprising this active compound may be use in the  
prevention and/or treatment of disorders in the CNS and related disturbances such as 5-  
10 hydroxytryptamine mediated disorders. Examples of such disorders are disorders in the  
central nervous system (CNS) and related disturbances such as mood disorders  
(depression, major depressive disorder, major depressive episodes, dysthymia, seasonal  
affective disorder, depressive phases of bipolar disorder), anxiety disorders (obsessive  
compulsive disorder, panic disorder with/without agoraphobia, social phobia, specific  
15 phobia, generalized anxiety disorder, posttraumatic stress disorder), personality disorders  
(disorders of impulse control, trichotillomania), obesity, anorexia, bulimia, premenstrual  
syndrome, sexual disturbances, alcoholism, tobacco abuse, autism, attention deficit,  
hyperactivity disorder, migraine, memory disorders (age associated memory impairment,  
presenile and senile dementia), pathological aggression, schizophrenia, endocrine disorders  
20 (e g hyperprolactinaemia), stroke, dyskinesia, Parkinson's disease, thermoregulation, pain,  
hypertension. Other examples of hydroxytryptamine mediated disorders are urinary  
incontinence, vasospasm and growth control of tumors (e g lung carcinoma).

Another aspect of the invention relates to the use of the oral immediated release dosage

25 form of the present invention in prevention and/or treatment of mood disorders, anxiety  
disorders, personality disorders, obesity, anorexia, bulimia, premenstrual syndrome, sexual  
disturbances, alcoholism, tobacco abuse, autism, attention deficit, hyperactivity disorder,  
migraine, memory disorders, pathological aggression, schizophrenia, endocrine disorders,  
stroke, dyskinesia, Parkinson's disease, thermoregulatory disorders, pain, hypertension,  
30 major depressive disorder, urinary incontinence, vasospasm and growth control of tumors.

A further aspect of the present invention relates to the use of the oral immediated release dosage form of the present invention in the manufacturing of a medicament for prevention and/or treatment of disorders in the CNS and related disturbances such as 5-hydroxytryptamine mediated disorders and any other disorders listed above.

5

A further aspect of the invention relates to a method for prevention and/or treatment of disorders in the CNS and related disturbances such as 5-hydroxytryptamine mediated disorders and any other disorders listed above, comprising administering to a mammal in need of such prevention and/or treatment oral immediated release dosage form of the 10 present invention, effective for said prevention and/or treatment.

The term "rapid" as used in this specification means within 60 minutes, preferably within 30 minutes.

The term "large scale" means a manufacturing scale in the range of "kilogram to multiton".

15

### Abbreviations

CNS	Central Nervous System
t	time (h)
20	$t_{1/2}$ plasma elimination half-life (h)
$C_{max}$	Maximum plasma drug concentration (nmol/L)
$t_{max}$	Time to reach maximum plasma drug concentration following drug administration (h)
HPC (LF)	Hydroxypropylcellulose (molecular weight approx. 95,000, pharm. grade)
25	PEG Polyethylene glycol
PVP	Polyvinylpyrrolidone
HPLC	High Pressure Liquid Chromatography

### Examples

30 The invention will now be illustrated by the following non-limiting examples.

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11 99-9

**Example 1:**

The following components, expressed as mg per capsule, were used; batch size 28000 capsules:

Active compound:	59
5 PVP K25	8.9
Croscarmellose sodium	17.9
Mannitol	93
Water	71.5
Magnesium stearate	0.45
10 Colloidal silicon dioxide	0.45

The active compound, (*R*)-*N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide monohydrobromide, were screened through a 0.5 mm square screen. PVP K 25 and croscarmellose sodium were added and all the ingredients  
15 were thereafter mixed in a Turbula mixer for 10 minutes at 30 rpm.

The powder mixture was then transferred to a high shear mixer. Mannitol, sieved though 0.5 mm square screen, was added and the powder was further mixed for 10 minutes at 150 rpm. This powder mixture was then granulated with water in the high shear mixer for 2 minutes and 45 seconds at 150 rpm. A chopper was used during the last 15 s at 2000 rpm. The formed wet granules were dried in a drying cabinet at +50°C for 5 hours. The granules were milled in an oscillating granulator through a screen of 1.00 mm. The dry powder mass was then mixed with colloidal silicon dioxide (screened through 0.5 mm) in a Turbula mixer for 3 minutes at 30 rpm. Magnesium stearate was added through a screen of 0.5 mm and the mixing was continued for further 45 seconds.  
25

The final homogeneous powder mixture was filled into hard gelatine capsules size no. 1, colour Swedish orange, in a capsule filling machine.

In order to test the release rate of the active drug compound from the capsules an *in vitro* dissolution of the capsule was accomplished by using the USP paddle method, 75 rpm.  
30 (Dissolution Test, USP 24)

Used conditions:

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Date: 11/10/83

Medium: acetate buffer, pH = 5.5, volume: 1000 ml, temperature: 37°C.

The following results were obtained:

Time (min)	Amount dissolved %
0	0
5	5
10	26
15	48
20	68
25	86
30	98
45	101
60	102

5   **Example 2:**

The following components, expressed as mg per capsule, were used; batch size 550 capsules:

Active compound:                         59

PVP K25                                     8.9

10   Mannitol                                 110.9

Water   30

Magnesium stearate                         0.45

Colloidal silicon dioxide                 0.45

15   In this experiment the composition was altered in order to show the effect of the disintegrant (croscarmellose sodium). The disintegrant was substituted with the release modifier mannitol, in equal amounts. The capsules in Example 2 was produced in the same manner as in Example 1, except that the capsule fill was done gravimetrically.

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The *in vitro* release rate of the active compound, (*R*)-*N*-(5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide monohydrobromide, from the dosage form of Example 2 was measured using the same method as in Example 1.

### **s      Conclusion:**

From the Examples 1 and 2 it is evident that with the oral dosage form according to the present invention an immeidated release is achieved only by using the disintegrant.

## 10 Bioavailability

A single dose bioavailability study was performed in healthy volunteers. Two different formulations of (*R*)-*N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide monohydrobromide were tested. One group of fasting 6 volunteers received (*R*)-*N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide monohydrobromide as an aqueous solution (n=6). The other group of 5 volunteers received (*R*)-*N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide monohydrobromide in an immediate release capsule (n=5). The composition of the capsule is according to Example 1, except that the concentration of the active compounds was lower (3.3%). The dose in both dosing groups was 15 mg (calculated as the base). Plasma samples were withdrawn prior to and up to 200 hours after drug administration (for solution dosing group up to 48 hours).

Determination of (*R*)-*N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide monohydrobromide in the plasma was performed using liquid chromatography-tandem mass spectrometry (LC-MS-MS). After oral administration of (*R*)-*N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide monohydrobromide, the following pharmacokinetic parameters of the corresponding base were estimated: maximum plasma drug concentration ( $C_{max}$ ), time to reach  $C_{max}$  following drug administration ( $t_{max}$ ), area under plasma concentration-time curve from zero to infinity ( $AUC_{(0-\infty)}$ ), terminal half-life ( $t_{1/2}$ ) and oral clearance (CL/F). The results are presented in Table A below.

**Table A. Pharmacokinetic data obtained after administration of an oral solution compared to the oral immeidated release dosage form of Example 1. Dose 15 mg (as the base)**

Dosing form		t <sub>max</sub> (hours)	C <sub>max</sub> (nmol/L)	t <sub>1/2</sub> (hours)	AUC (0-∞) (nmol <sup>2</sup> ·h/L)	CL/F (L/h)
<b>Oral solution</b>	Mean	5.0	31.7	35.2	1314	26.3
	(n=6) SD	2.2	13.4	8.0	290	6.1
	Median	5.5	26.0	33.7	1295	25.9
	Range	2.0 - 8.0	20.3 - 49.1	25.7 - 47.6	918 - 1744	19.2 - 36.4
<b>Capsules 3 x 5 mg</b>	Mean	4.6	32.9	37.1	1295	26.2
	SD	1.7	8.2	6.2	176	3.6
	Median	5.0	35.7	35.4	1254	26.7
	Range	3.0 - 7.0	23.0 - 41.0	30.2 - 44.1	1084 - 1479	22.6 - 30.8

5 The results show that the oral immeidated release dosage form according to the present invention provides a blood plasma profile of the active compound similar to when the active compound is administered orally in an aqueous solution. This is valid for both the t<sub>max</sub> and the C<sub>max</sub>. The initial rise in blood plasma concentration is achieved by administration of the active compound in the oral immeidated release dosage form of the present invention.

10 The present invention relates to the oral immeidated release dosage form of the present invention, whereby the dosage form upon administration provides t<sub>max</sub> for (R)-N-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide monohydrobromide between 3 to 7 hours.

## CLAIMS

1. An oral immeidated release dosage form comprising *N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide as the active compound, in

s the form of the free base or pharmaceutically acceptable salts, thereof, at least one disintegrant, at least one binder, and optionally other excipients.

2. An oral immeidated release dosage form comprising

*N*-[5-methyl-8-(4-methylpiperazin-1-yl)-

3 to 35 % (w/w)

1,2,3,4-tetrahydro-2-naphthyl]-4-

morpholinobenzamide

Disintegrants 5 to 20% (w/w)

Binders 1 to 10 % (w/w)

Other excipients up to 100% (w/w)

10 3. The oral immeidated release dosage form according to claims 1 or 2, wherein the active compound is (*R*)-*N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide.

15 4. The oral immeidated release dosage form according to any one of claims 1 to 3, wherein the salt of (*R*)-*N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide is (*R*)-*N*-[5-methyl-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide monohydrobromide.

20 5. The oral immeidated release dosage form according to any one of claims 1 to 4, wherein the disintegrants are selected from the group consisting of croscarmellose sodium, sodium starch glycollate, crospovidone, microcrystalline cellulose, soy polysaccharide, starch, alginic acid, magnesium aluminium silicate and amberlite resins.

25 6. The oral immeidated release dosage form according to claim 5, wherein the disintegrant is croscarmellose sodium.

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7. The oral immeidated release dosage form according to any one of claims 1 to 6, wherein the binders are selected from the group comprising of hydroxypropyl cellulose, microcrystalline cellulose, polyvinylpyrrolidone, gelatine, polyethylene glycol, glycetylbehenate, glycerylmonostearate and carnauba wax or a mixture thereof.

5

8. The oral immeidated release dosage form according to claim 7, wherein the binder is polyvinylpyrrolidone.

9. The oral immeidated release dosage form according to any one of claims 1 to 8, wherein  
10 the other excipients are lubricants, release modifying agents and flow condition agents.

10. The oral immeidated release dosage form according to claim 9, wherein the lubricants are selected from the group of magnesium stearate powder, sodium stearyl fumarate, stearic acid, polyethylene glycol and talc.

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11. The oral immeidated release dosage form according to claim 9, wherein the release modifying agents are selected from the group of lactose, mannitol, sorbitol, calcium phosphate, aluminium silicate, paraffin, carboxypolymethylene, carboxyvinyl polymer, acrylic acid polymer, ethyl cellulose and polyethylene glycol.

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12. The oral immeidated release dosage form according to claim 9, wherein the flow condition agent is colloid silicon dioxide.

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13. The oral immeidated release dosage form according to any one of claims 1 to 12, wherein the ratio of active compound to disintegrants is from 5:1 to 1:2, preferably from 3:1 to 1:1.

14. The oral immeidated release dosage form according to any one of claims 1 to 13, wherein the weight ratio of active compound to binders may be from 8:1 to 1:2.

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15. The oral immeidated release dosage form according to any one of claims 1 to 14, wherein the dosage form is in the form of a tablet or a capsule.

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16. The oral immediated release dosage form according to any one of claims 1 to 15, whereby the dosage form has a mean dissolution profile *in vitro*, in 50 nM acetate buffer, pH of 5.5, using USP Paddle method at 75 rpm, such that at least 80 % of the active compound is released within 30 minutes.

17. Processes for the manufacture of an oral immediated release dosage form according to any one of claims 1 to 15 characterized by, method A, comprising the steps:
- 10 Ai) mixing the active compound with the disintegrant, binders and optionally lubricants, release modifying agents and other excipients,
  - Aii) forming the obtained dry powder mixture into a suitable solid dosage form, or,
  - method B, comprising the steps:
  - 15 Bi) mixing the active compound with the disintegrant and optionally binders and other excipients,
  - Bii) granulating said mixture,
  - Biii) optionally drying the obtained granules,
  - Biv) mixing the granules with other excipients,
  - 20 Bv) filling the obtained dry powder mixture into suitable solid dosage form.

18. Use of an oral immediated release dosage form according to any one of claims 1 to 15 for use in therapy.

- 25 19. The use according to claim 18 for the prevention and/or treatment of disorders in the central nervous system and related disturbances.
20. The use according to claim 18 for the prevention and/or treatment of mood disorders, anxiety disorders, personality disorders, obesity, anorexia, bulimia, premenstrual syndrome, sexual disturbances, alcoholism, tobacco abuse, autism, attention deficit, hyperactivity disorder, migraine, memory disorders, pathological aggression,

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schizophrenia, endocrine disorders, stroke, dyskinesia, Parkinson's disease, thermoregulatory disorders, pain and hypertension.

21. The use according to claim 18 for the prevention and/or treatment of major depressive disorder.
22. The use according to claim 18 for the prevention and/or treatment of urinary incontinence, vasospasm and growth control of tumors.
23. The use according to claim 18 for the prevention and/or treatment of 5-hydroxytryptamine mediated disorders.
24. Use of an oral immeidated release dosage form according to any one of claims 1 to 15, in the manufacturing of a medicament for prevention and/or treatment of disorders in the CNS and related disturbances.
25. A method for prevention and/or treatment of disorders in the central nervous system and related disturbances, comprising administering to a mammal in need of such prevention and/or treatment oral immeidated release dosage form according to any one of the claims 1 to 15, effective for said prevention and/or treatment.
26. An oral immeidated release dosage form according to any one of claims 1 to 15, whereby the dosage form upon administration provides  $t_{max}$  for (R)-N-[5-methyl]-8-(4-methylpiperazin-1-yl)-1,2,3,4-tetrahydro-2-naphthyl]-4-morpholinobenzamide monohydrobromide between 3 to 7 hours.
27. Use of disintegrants in preparing an oral immediate release dosage form of an active compound that forms an upon contact with water, at acid, neutral and basic pH.

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**ABSTRACT**

The present invention relates to a solid oral immediate release dosage form of a pharmaceutically active compound, *N*-[(1,2,3,4-tetrahydro-5-methyl-8-(4-methylpiperazin-1-yl)-2-naphthyl]-4-morpholinobenzamide, in the form of the free base or pharmaceutically acceptable salts thereof. The invention further relates to processes for preparing said dosage form, the use of said dosage form and a method of prevention and/or treatment of CNS disorders and related medical disturbances using said dosage form.

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